AMENDMENT

In the Specification:

Please delete the paragraph on page 16, lines 12-18, and replace it with the following paragraph:

Figure 3A **(SEQ ID NOS 3-10, respectively in order of appearance)** shows a protein spot which increases in intensity in drug treated cells and drug resistant cells, as well as analysis of the protein sequence showing that it is triosephosphate isomerase (TIM, or TPI). Drug treated cells were exposed to doxorubicin for 72 hrs and the 10% resulting live cells were purified on gradients and total cell extracts were made from these cells (labeled as treated or drug treated cells) and ran on 2D gels. The 2D gels from these latter extracts were compared to untreated Ovarian cells (drug sensitive cells or controls) as well as to drug resistant cells that have been selected over a period of time and are stably resistant.

Please delete the paragraph on page 61, line 24, to page 62, line 12, and replace it with the following paragraph:

Enzymically degradable linkers may also be used to link therapeutic agents to antibodies or other localizing agents. The gold standard for attaching and releasing drugs from macromolecules is a linker which is stable in serum but can be cleaved intracellularly by specific enzymes. Linkers of this type have been described containing a variety of amino acids. Some of these linkers have been used in targeted drug conjugates with antibodies, but others only in polymer-drug conjugates. Cleavable amino acid pro-drugs of daunomycin (Dau) were first produced by Levin and Sela (Levin, *et al.*, (1979) FEBS Lett. 98:119-122), although these were designated as low-molecular weight pro-drugs. The first systematic studies investigating amino acid sequences and lengths for lysosomal digestion were reported by (Masquelier et al. (1980) J. Med. Chem. 23:1166-1170). These studies identified an Ala-Leu-Dau derivative which could be converted back to the free drug by lysosomal hydrolases in 2 h. The activity was ascribed to a lysosomal dipeptidyl aminopeptidase. While these dipeptide derivatives were much less potent than Dau in vitro, they showed greater potency in vivo (Baurain, *et al.*, (1980) J. Med. Chem. 23:1171-1174). Further work reported by this group (Trouet, *et al.*, (1982) Proc. Natl. Acad. Sci. USA 79:626-629) resulted in conjugates in which daunorubicin was linked to succinylated serum albumin by a spacer arm of one to four amino acids. A minimum tri or peptide spacer was found to be essential for good release of drug. A release of 75% of free drug

was achieved in 8 h with an albumin conjugate with an Ala-Leu-Ala-Leu-Dau linkage **(SEQ ID NO: 11)**, which was stable in the presence of serum (only 2.5% drug released in 24 h). No drug was released by lysosomal enzymes from Dau conjugated to succinylated serum albumin without a peptide spacer.

Please delete the paragraph on page 62, lines 13-20, and replace it with the following paragraph:

Another tetrapeptide spacer was derived from a long collaboration between Duncan and Kopecek, in which the release of *p*-nitroaniline as a model drug from poly[*N*-(2-hydroxypropyl)methacrylamide] co-polymers was investigated (described in Duncan [(Duncan, (1986) CRC Crit. Rev. Biocompat. 2:127-145)]). These studies resulted in a greater understanding of lysosomal enzyme specificity and the development of a Gly-Phe-Leu-Gly-Dau linker **(SEQ ID NO: 12)** which released 80% of bound *p*-nitroaniline over a 50-h incubation period. Daunomycin was subsequently coupled to the polymer delivery systems (Duncan, et al., (1987) Br. J. Cancer 55:165-174) and as antibody carrier drug conjugates.

Please delete the paragraph on page 62, lines 21-30, and replace it with the following paragraph:

A tetrapeptide spacer has been incorporated into monoclonal antibody-methotrexate conjugates by (Umemoto, *et al.*, (1989) Int. J. Cancer 43:677-684). This is a MTX-Leu-Ala-Leu-Ala-hydrazide linker **(SEQ ID NO: 13)** based on the tetrapeptide described by Trouet. However, in Trouet's study the Dau was attached to the C-terminal of the peptide, and in this conjugate MTX was attached to the N terminal of the peptide. In addition there is also a hydrazide incorporated into the linkage which may give some acid-sensitive release of the drug-linker part of the conjugate. No studies were reported on the effect of lysosomal enzymes on this linker, and what products were released, nor the rate of release of products. However, these linkers gave a substantial increase in efficiency of the conjugate compared to directly linked MTX, and release was shown by inhibitors such as leupeptin to be lysosomally mediated.